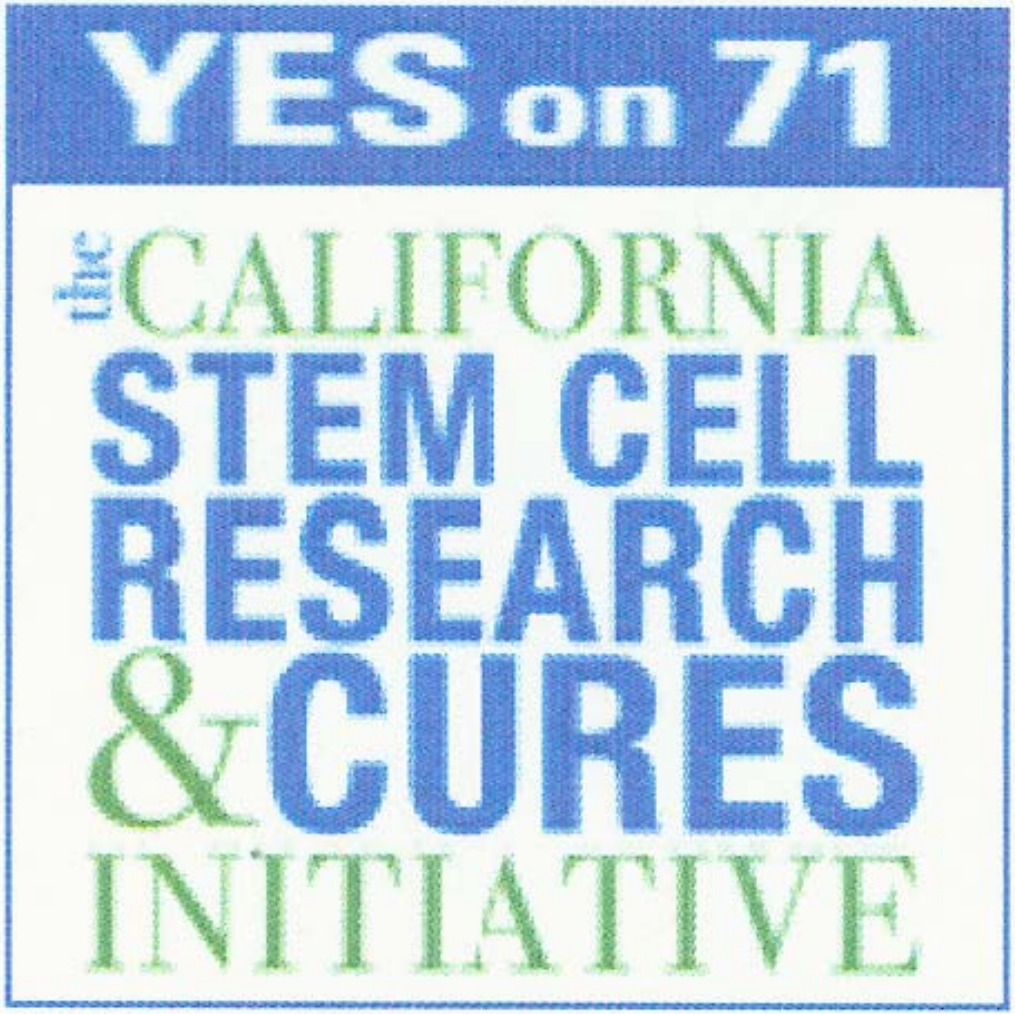
Stem cells: looking back and ahead



Stem cells: laboratory to the patient

What do we need to know or think about?

1. The cells: obtaining the proper cells, and then learning how to utilize them in preclinical models

2. The host: learning how stem cells, or their derivatives, behave when introduced into tissues/organs

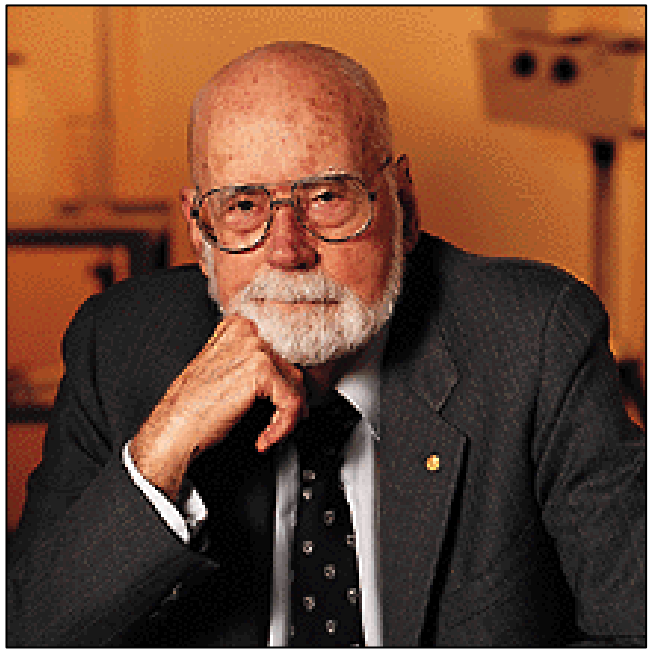
3. The disorders we wish to treat: what are the most promising conditions for treatment with stem cells or their derivatives?

4. Transitioning to the clinic: synthesizing the above, and navigating clinical regulatory environment, ethics, etc.

Some historical examples to consider

1. Bone Marrow Transplantation: a cellular, stem cell therapy now 50 yrs old. How did it proceed in the “early days”?
2. Assisted Reproduction: cellular manipulation that emerged on the public scene quickly
3. Gene Therapy: cellular and molecular therapy with “checkered” history. What might we learn?

BMT: the early days



In 1955, at the invitation of Dr. Joseph Ferrebee I went to the Mary Imogene Basset Hospital in Cooperstown, N. Y., an affiliate of Columbia University. Immediately, we began to work on marrow transplantation in human patients and in the dog, as an outbred animal suitable for clinical care comparable to human patients. Except for an occasional patient with an identical twin, we quickly learned that allogeneic marrow transplants in man were going to be very difficult. Joe Ferrebee and I and our young colleagues concentrated on working with our dogs on many aspects of marrow transplantation. The long cold winters, absence of commuting problems and opportunity for long discussions were conducive to our work. Those years had a deep and abiding influence on subsequent work since most of the basic concepts were laid out during that time.

E. D. Thomas

Nobel Lecture 1991

BMT: rapid progress in the early days

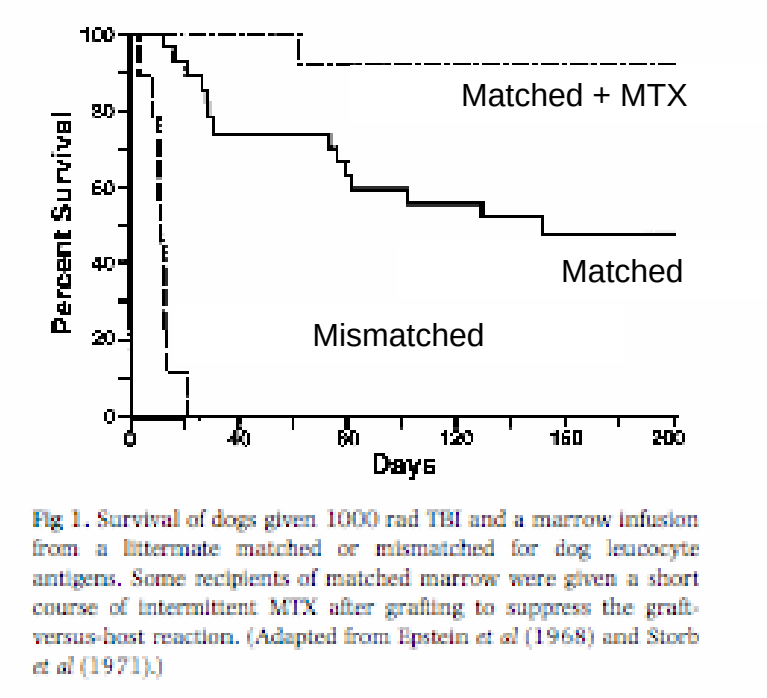


Fig 1. Survival of dogs given 1000 rad TBI and a marrow infusion from a littermate matched or mismatched for dog leucocyte antigens. Some recipients of matched marrow were given a short course of intermittent MTX after grafting to suppress the graft-versus-host reaction. (Adapted from Epstein *et al* (1968) and Storb *et al* (1971).)

Dogs 1971

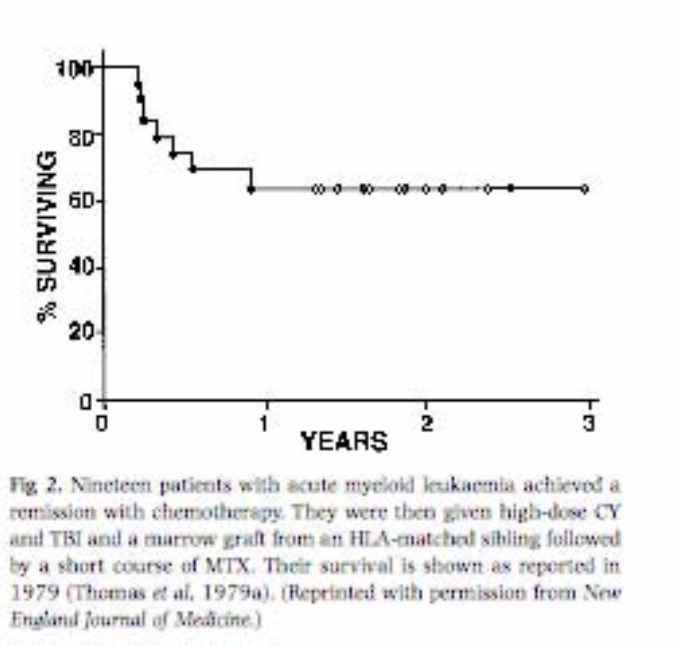


Fig 2. Nineteen patients with acute myeloid leukaemia achieved a remission with chemotherapy. They were then given high-dose CY and TBI and a marrow graft from an HLA-matched sibling followed by a short course of MTX. Their survival is shown as reported in 1979 (Thomas *et al*, 1979a). (Reprinted with permission from *New England Journal of Medicine*.)

Human leukemia patients 1979

Bone Marrow Transplantation

- A true stem cell success story
- Founded on strong science and trial-and-error
- Developed in animal models, yet transition to clinical experiments occurred quite early on
- Initial scientific advances largely out of the public eye
- Initial failures overcome by persistence of committed investigators
- At least 20 yr timeframe before clearly successful
- Now a mainstay of medicine

An Interesting Date in Medicine

July 27, 1978

Two bits of medical news:

- Prenatal genetic diagnosis by DNA analysis
- Assisted reproduction announcement

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
LinkOut
My NCBI (Cubby)

Related Resources
Order Documents
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

1: N Engl J Med. 1978 Jul 27;299(4):166-72. Related Articles, Links

Application of endonuclease mapping to the analysis and prenatal diagnosis of thalassemias caused by globin-gene deletion.

Orkin SH, Alter BP, Altay C, Mahoney MJ, Lazarus H, Hobbins JC, Nathan DG.

We applied a recently developed and more direct technic to diagnose thalassemia syndromes associated with deletion of particular globin structural genes and to assess a fetus at risk for one of those conditions, deltabeta-thalassemia. The method allows assessment of the globin genes present in total cellular DNA and is applicable to amniotic-fluid cell DNA. Cellular DNA fragments produced by cleavage using two specific restriction endonucleases are separated on the basis of size by agarose-gel electrophoresis, and the distribution of specific sequences among the DNA fragments determined by molecular hybridization. We observed the total deletion of alpha-globin genes in homozygous alpha-thalassemia (hydrops fetalis with hemoglobin Bart's) and the deletion of particular beta and beta-like sequences in cases homozygous for hereditary persistence of fetal hemoglobin and deltabeta-thalassemia. Analysis of amniotic-fluid cell DNA from a fetus at risk for deltabeta-thalassemia demonstrated the feasibility of these improved methods for antenatal diagnosis. The molecular studies confirmed the diagnosis predicted by analysis of fetal blood and established at birth.

"All the News That's Fit to Print"

The New York Times

LATE CITY EDITION

Weather: Hazy, storms by evening; clearing tonight. Sunny tomorrow. Temperature range: today 89-67, yesterday 77-64. Details on page D15.

VOL. CXXVII . . . No. 44,014 NEW YORK, THURSDAY, JULY 27, 1978 20 CENTS

161 INSPECTORS HIRED BY KOCH TO COMBAT AGENCY CORRUPTION

INCOMPETENCE ALSO A TARGET

City's Employees Told They Must Report Any Malfeasance — Gotbaum Attacks Plan

By EDWARD RANZAL

Mayor Koch hired 161 new inspectors yesterday for an "overseer" program meant to root out corruption and incompetence in 30 New York City agencies.

In an executive order, he also strengthened employee guidelines for standards and discipline and made it obligatory for the agencies' 225,000 employees to inform superiors of corruption, criminal activity or conflicts of interest among fellow workers.

An employee who knows of criminal activity by another city employee, or people doing business with the city, but fails to report it, could be dismissed, said Harvey Lapkin, the Investigation Commissioner.

Gotbaum Is Critical

"While the overwhelming majority of city employees, who are honest and perform their duties competently, have nothing to fear from this program," the Mayor said, "I want to serve notice on the small number of employees who violate the public trust that they have no place in this administration."

Victor Gotbaum, head of District Council 37, the largest municipal union, promptly criticized the program as "destructive."

"Show and tell," he said of the informer requirement.

Lindsay Also Named Inspectors

The program is not new to the city. Former Mayor John V. Lindsay appointed inspectors general to monitor the conduct of city employees in major mayoral agencies. In 12 years the program has grown to cover 11 agencies.

Under Mayor Koch's program, 25 inspectors general, 17 deputies and 200 confidential inspectors will seek to end corrupt practices, misconduct and incompetence in the 30 agencies.

The Mayor announced his program at a news conference in the City Council Chamber after he swore in new inspectors general and their deputies.

After the announcement, Mr. Gotbaum called the Mayor's action "kind of sad," saying it was not going to "make for job satisfaction among employees."

During his election campaign Mr. Koch spoke out about inequitable and dishonesty among municipal workers. In his first days in office he promised to adopt the program he put into action officially yesterday. Since then relations between Mr. Koch and some city labor leaders have been edgy.

Besides the conflicts that have been

Continued on Page D16, Column 6

ACTIVIST FREED: Mariya Slepak in Moscow after she received a suspended sentence. Page A3.

INSIDE

Trade Deficit Cut in June

The Commerce Department said the nation's trade deficit had been halved in June but had worsened sharply in the first half of the year. Page D8.

Dr. Robert Edwards, left, and Dr. Patrick Steptoe at news conference yesterday in Manchester, England

Scientists Praise British Birth as Triumph

Early Insertion of Embryo Into Womb Is Linked to Successful Gestation

Doctors' Success in Conception in the Laboratory Intensifies the Debate Over Reproductive Control

By ROY REED

By WALTER SULLIVAN

LONDON, July 26 — Scientists applauded, English churchmen nodded a qualified approval and the British press turned somersaults today to welcome the world's first baby born from an egg fertilized in a laboratory.

The 5-pound-12-ounce baby, a girl born slightly prematurely, was delivered by Caesarean section last night at the Oldham General Hospital in Lancashire. Dr. Patrick C. Steptoe was in charge of the delivery. A hospital spokesman said the baby was "quite normal."

At a news conference today, Dr. Robert G. Edwards, a Cagbridge University specialist in reproductive physiology, who was one of the two physicians involved in the birth, said that the embryo was placed in the womb of Mrs. Brown two and a half days after fertilization. This was in contrast to the four and a half days that had elapsed before the embryo was placed inside the womb in earlier attempts, he said. When the embryo was placed in Mrs. Brown's womb, he added, it had only reached the eight-cell stage.

Supported Earlier Speculation

This supported earlier speculation that such early insertion, which was previously thought to endanger the embryo, had contributed to the procedure's success.

The baby was gestated in the normal manner, with placenta and umbilical cord linking it to the mother's blood supply. However, where unusual birth conditions are anticipated, Caesarean deliveries have become the practice to minimize the risk of harm to the baby.

The doctors had known the sex of the child for some time, but Mrs. Brown had insisted that she not be told. "After waiting for years for this wonderful thing to happen, I do not want to be cheated of the final thrill," she said.

Church leaders both here and in other countries generally welcomed the achievement, but with qualifications, especially from Roman Catholic leaders. [Page A16.]

Leo Abse, a Labor Party Member of Parliament, urged the regulation of

Continued on Page A16, Column 2

LONDON, July 26 — Scientists applauded, English churchmen nodded a qualified approval and the British press turned somersaults today to welcome the world's first baby born from an egg fertilized in a laboratory.

The 5-pound-12-ounce baby, a girl born slightly prematurely, was delivered by Caesarean section last night at the Oldham General Hospital in Lancashire. Dr. Patrick C. Steptoe was in charge of the delivery. A hospital spokesman said the baby was "quite normal."

At a news conference today, Dr. Robert G. Edwards, a Cagbridge University specialist in reproductive physiology, who was one of the two physicians involved in the birth, said that the embryo was placed in the womb of Mrs. Brown two and a half days after fertilization. This was in contrast to the four and a half days that had elapsed before the embryo was placed inside the womb in earlier attempts, he said. When the embryo was placed in Mrs. Brown's womb, he added, it had only reached the eight-cell stage.

Supported Earlier Speculation

This supported earlier speculation that such early insertion, which was previously thought to endanger the embryo, had contributed to the procedure's success.

The baby was gestated in the normal manner, with placenta and umbilical cord linking it to the mother's blood supply. However, where unusual birth conditions are anticipated, Caesarean deliveries have become the practice to minimize the risk of harm to the baby.

The doctors had known the sex of the child for some time, but Mrs. Brown had insisted that she not be told. "After waiting for years for this wonderful thing to happen, I do not want to be cheated of the final thrill," she said.

Church leaders both here and in other countries generally welcomed the achievement, but with qualifications, especially from Roman Catholic leaders. [Page A16.]

Leo Abse, a Labor Party Member of Parliament, urged the regulation of

Continued on Page A16, Column 5

Other critics have said that, in a world should concentrate on how to prevent births rather than encourage them.

This is the last of three articles on the implanting of human embryos and its implications.

Questions about the medical procedures and the possibility of birth defects have been raised also. And there is considerable controversy involving the destruction of embryos that attempts at implantation could entail.

What Dr. Steptoe and Dr. Edwards did was enable Lesley Brown to become pregnant despite a defect in her oviducts. Mrs. Brown gave birth last night in Oldham, England, to a healthy girl that the Browns named Louise today. The pre-

Doctors Isolate a Human Gene, Allowing Birth-Defect Detection

BOSTON, July 26 — For the first time, doctors have been able to identify a single gene among the millions in a human cell and can now see whether an unborn baby is missing certain parts of its genetic blueprint, a team of researchers reported today.

The report, in The New England Journal of Medicine, is the first example of applying some of the tools of gene-cutting, part of what is called recombinant DNA technology, to finding and understanding hereditary birth defects while a child is unborn.

Achievement Is Praised

Dr. Arthur W. Nienhuis of the National Heart, Lung and Blood Institute, who wrote an editorial in the journal on the implications of the achievement, said: "This is the first direct examination of the gene. The power of the technique is extraordinary, but the actual execution of it once mastered is not terribly difficult."

While the technique so far has allowed detection of only a rare group of genetic diseases, researchers predicted that within a few years they will have the genetic knowledge enabling them to detect more common ones, perhaps even cystic fibrosis.

Scientists estimate that there are three million to four million genes in each human cell. The team of researchers from Harvard and Yale Universities and the Hacettepe University in Turkey reported being able to produce an image of the gene that directs production of hemoglobin, which carries oxygen in the blood.

Thus, the team said, doctors can now detect certain debilitating and sometimes fatal forms of anemia, caused by

Continued on Page A16, Column 3

New York City Announces Moves To Halt Illegal Conversion of Lofts

By JOSEPH P. FRIED

New York City officials, announced plans yesterday to prevent further illegal conversions of factory buildings to residential use and to bring "into compliance with fire, health and safety codes" the 1,000 structures that have already been illegally converted.

Under plans disclosed by Mayor Koch and City Councilman Thomas J. Manton of Queens, head of the Council's

whatever deficiencies prevent the structures from meeting health and safety standards, the Mayor and Mr. Manton said.

These and other steps to deal with problems stemming from the increasing number of conversions of lofts to residential use were outlined in an "action plan" on the issue that was drawn up by a Koch ad-

Egyptians Order Israel's Mission To Leave Today

By WILLIAM E. FARRELL

JERUSALEM, July 26 — Prime Minister Menachem Begin said tonight that Israel had been ordered by Egypt to withdraw, by tomorrow, its military mission based in Egypt since January.

The negotiation support group went to Egypt when talks opened on peace issues, after President Anwar el-Sadat's visit to Jerusalem. It remained in Egypt even though the peace talks quickly became stalemated.

The order for the withdrawal of the 18 middle-rank military technicians and communications specialists was made after a meeting of the National Security Council in Cairo.

[Egyptian War Ministry officials confirmed in Cairo that the Israeli mission had been ordered to leave the country. They said the action reflected a Cairo decision to avoid further direct contacts until Israel adopted a new position on peace talks.]

'We Shall Do So,' Begin Says

Mr. Begin, appearing on television, seemed unruffled by the Egyptian order, implying that it was part of a new war of nerves by Cairo in the strained peace maneuvering. He urged Israelis to be patient, saying: "I don't minimize anything. I appreciate all Israelis to have strong nerves."

Mr. Begin said he received the order for the recall of the Israeli group a few hours earlier. "We shall do so," Mr. Begin said.

"Welcome home," he said in reference to the small Israeli mission, whose members spent much of their time at a military base near Alexandria playing volleyball and cards. The mission had been a lingering symbol of direct Egyptian-Israeli contact in the uncertain period that

Continued on Page A3, Column 1

Justice Dept. Supports Detroit Police Quotas

By STEVEN V. ROBERTS

WASHINGTON, July 26 — In its first interpretation of the Supreme Court's Bakke decision, the Justice Department has urged approval of an affirmative action program that sets strict numerical quotas for the promotion of blacks in the Detroit police department.

The Court's decision last month did not require public agencies to be "color-blind," the department argued, and did not disturb previous rulings that required such agencies to take positive steps to remedy the effects of past discrimination.

The Justice Department's comments come in a brief as a friend of the court filed today with the United States Court of Appeals for the Sixth Circuit in a case called Detroit Police Officers Association v. Coleman A. Young. In that case, white police officers challenged an affirmative action plan that mandated the police department to promote one black to the rank of sergeant for every white promoted. Last February, the plan was ruled unconstitutional by Judge Fred W. Kaess of Federal District Court.

The department's brief had political as well as legal implications. Supporters of

Continued on Page B10, Column 1

CURBS ON RHODESIA UPHELD BY SENATE, BUT CONDITIONALLY

CARTER COULD LIFT SANCTIONS

He Must Determine Free Vote Has Occurred and New Regime Is Intent on Negotiations

By GRAHAM HOVEY

WASHINGTON, July 26 — The Senate rejected a move to repeal economic sanctions against Rhodesia today, but then decisively adopted a compromise measure setting conditions under which the President could be required to lift the sanctions in the future.

The sponsors of the compromise amendment to the International Security Assistance Bill insisted that it was designed to keep the United States on a

Roll-call vote on Rhodesia, page A6.

"moderate middle course" between the current Rhodesian Government, led by Prime Minister Ian D. Smith, and the Patriotic Front, the nationalist group that is waging guerrilla war to bring down that Government. Tonight, the Senate passed the full aid bill, 73 to 13.

Despite the "moderate" nature of the amendment on Rhodesian sanctions, Administration officials fear that its language would make it appear that the United States is siding with Mr. Smith and the three black members of his transitional Government, who are committed to establishing majority rule after free elections planned for December.

Good Faith an Issue

In effect, the amendment would require President Carter to lift the sanctions, but only after he had determined that a Rhodesian government had been established through free elections under impartial international observation, and that it had committed itself to negotiate in good faith with the guerrilla leaders.

The sanctions, voted by the United Nations Security Council in 1966 and 1968, have the force of American law. They ban all trade with Rhodesia.

The sponsors of today's amendment, Senator Clifford P. Case of New Jersey and Jacob K. Javits of New York, both Republicans, argued that their proposal would eliminate fears in this country and in Africa that the United States was siding with the Patriotic Front guerrilla leaders, Joshua Nkomo and Robert Mugabe.

Reluctant to Negotiate

The transitional Government has equal numbers of white and black ministers and had promised to hold elections based on universal suffrage in December, but thus far have been unwilling to negotiate with the guerrillas.

The Case-Javits amendment was adopted today by 59 to 36, but the most critical test came on an earlier movement to table it, which the Senate defeated, 57 to 39. Its adoption sidetracked the amendment of Senator Jesse Helms, Republican of North Carolina, who proposed an immediate end of sanctions.

Senator Helms withdrew his amendment after a substitute proposal by Senator John C. Danforth, Republican of Missouri, had been defeated, 54 to 42, in the closest roll-call vote of the day.

Mr. Danforth had proposed that the

Continued on Page A6, Column 1

July 27, 1978

Dr. Robert Edwards, left, and Dr. Patrick Steptoe at news conference yesterday in Manchester, England

Scientists Praise British Birth as Triumph

Early Insertion of Embryo Into Womb Is Linked to Successful Gestation

By ROY REED
Special to The New York Times

LONDON, July 26 — Scientists applauded, English churchmen nodded a qualified approval and the British press turned somersaults today to welcome the world's first baby born from an egg fertilized in a laboratory.

The 5-pound-12-ounce baby, a girl born slightly prematurely, was delivered by Caesarean section last night at the Oldham General Hospital in Lancashire. Dr. Patrick C. Steptoe was in charge of the delivery. A hospital spokesman said the baby was "quite normal."

At a news conference today, Dr. Robert G. Edwards, a Cambridge University specialist in reproductive physiology, who was one of the two physicians involved in the birth, said that the embryo was placed in the womb of Mrs. Brown two and a half days after fertilization. This was in contrast to the four and a half days that had elapsed before the embryo was placed inside the womb in earlier attempts, he said. When the embryo was placed in Mrs. Brown's womb, he added, it had only reached the eight-cell stage.

Supported Earlier Speculation

This supported earlier speculation that such early insertion, which was previously thought to endanger the embryo, had contributed to the procedure's success.

The baby was gestated in the normal manner, with placenta and umbilical cord linking it to the mother's blood sup-

Doctors' Success in Conception in the Laboratory Intensifies the Debate Over Reproductive Control

By WALTER SULLIVAN
Special to The New York Times

LONDON, July 26 — The first authenticated birth of a baby conceived in a laboratory, an event that comes on the heels of other developments in reproductive control, has intensified debate among scientists that touches such issues as the sanctity of life.

Early in this decade, when the work of the two men responsible for the birth, Dr. Robert G. Edwards and Dr. Patrick C. Steptoe, first became widely known, it was denounced by a number of scientists, theologians and others. In Britain a winner of the Nobel Prize in chemistry termed the research a "stunt" and proposed that "the whole nation should decide whether or not these experiments should continue."

Some of the most vehement critics, warning of dire social consequences, have contended that procreation is sacred and that the performance of its most critical step in a laboratory degrades humanity.

Other critics have said that, in a world suffering from overpopulation, scientists should concentrate on how to prevent births rather than encourage them.

This is the last of three articles on the implanting of human embryos and its implications.

Questions about the medical procedures and the possibility of birth defects have been raised also. And there is considerable controversy involving the destruction of embryos that attempts at implantation could entail

What Dr. Steptoe and Dr. Edwards did was enable Lesley Brown to become pregnant despite a defect in her oviducts. Mrs. Brown gave birth last night in Oldham, England, to a healthy girl that the Browns named Louise today. The pregnancy was reportedly achieved by

Continued on Page A16, Column 5

Doctors Isolate a Human Gene, Allowing Birth-Defect Detection

By United Press International

BOSTON, July 26 — For the first time, doctors have been able to identify a single gene among the millions in a human cell and can now see whether an unborn baby is missing certain parts of its genetic blueprint, a team of researchers reported

detection of only a rare group of genetic diseases, researchers predicted that within a few years they will have the genetic knowledge enabling them to detect more common ones, perhaps even cystic fibrosis.

position on peace talks.]

'We Shall Do So,' Begin Says

Mr. Begin, appearing on television, seemed unruffled by the Egyptian order, implying that it was part of a new war of nerves by Cairo in the strained peace maneuvering. He urged Israelis to be patient, saying: "I don't minimize anything. I advise all Israelis to have strong nerves."

Mr. Begin said he received the order for the recall of the Israeli group a few hours earlier. "We shall do so," Mr. Begin added.

"Welcome home," he said in reference to the small Israeli mission, whose members spent much of their time at a military base near Alexandria playing volleyball and cards. The mission had been a lingering symbol of direct Egyptian-Israeli contact in the uncertain period that

Continued on Page A3, Column 1

Justice Dept. Supports Detroit Police Quotas

By STEVEN V. ROBERTS
Special to The New York Times

WASHINGTON, July 26 — In its first official interpretation of the Supreme Court's Bakke decision, the Justice Department has urged approval of an affirmative action program that sets strict numerical quotas for the promotion of blacks in the Detroit police department.

The Court's decision last month did not require public agencies to be "color-blind," the department argued, and did not disturb previous rulings that required such agencies to take positive steps to remedy the effects of past discrimination.

The Justice Department's comments came in a brief as a friend of the court filed today with the United States Court of Appeals for the Sixth Circuit in a case

RELIGIOUS LEADERS DIFFER ON IMPLANT

Catholics Critical of Conception Outside the Body, but Many Other Groups Endorse It

By GEORGE VECSEY

Roman Catholic leaders criticized all forms of artificial insemination yesterday, but Jewish, Moslem and Protestant figures could see a laboratory-induced conception no less an both husband and wife were the parents of the child.

The religious leaders and theologians were responding to the birth in England Tuesday night of the first baby known to have been conceived outside the body.

All the religious authorities interviewed expressed concern, however, about any possible broader uses of the technique for genetic engineering, and most expressed the fear that laboratory insemination could lead to women bearing other women's children. Others were concerned that more abortions might result from laboratory inseminations.

"I was quite touched by the passion of this woman to have a baby at a time when many women are choosing not to have children," said Blu Greenberg, an Orthodox Jewish writer, who is an advocate of women's rights.

A Reminder of Hannah

"In her determination, she reminded me of the Biblical heroine Hannah, mother of Samuel, who cried at the temple gates until God promised her she would have a child in the next year," Mrs. Greenberg, a mother of five, said.

The response from the Vatican, the headquarters of the world's 540 million Roman Catholics, was based on the same reasoning that the church has used to oppose artificial contraception.

The Rev. Pierfrancesco Pastore, a Vatican spokesman who noted that he was speaking personally, said, "Fecundation must be carried out according to nature and through reciprocal and responsible love between a man and a woman."

In the United States, Bishop Thomas C. Kelly, the general secretary of the National Council of Catholic Bishops, issued a statement that said in part:

"The Christian morality has insisted on the importance of protecting the process by which human life is transmitted. The fact that science now has the ability to alter this process significantly does not mean that, morally speaking, it has the right to do so."

A Somewhat Different View

A somewhat different view was taken by the Rev. Richard A. McCormick, a professor of Christian ethics at the Kennedy Institute of Georgetown University.

"If someone were to approach me about artificial insemination in which the husband were the donor, I would not have the certainty to say it's wrong," Professor McCormick said.

He noted that Pope Pius XII made four separate statements against artificial insemination from 1949 to 1956, but he added, "Since that time, there has been a long second look, a rethinking that it can be justified."

Father McCormick said that he would be raised on September 6 at a meeting of the Ethical Advisory Board, of which he is a member. He said he expected that the board's view would be used when research groups in the United States pursued grants to duplicate the British medical success.

'Remarkable Scientific Achievement'

Dr. C. Everett Koop, surgeon-in-chief at Children's Hospital in Philadelphia, who is a Presbyterian elder and an author on bioethics, praised the "remarkable scientific achievement." He added, "Since I believe that life begins at conception, I must ask what happens to the baby when it came to cancel the experiment and he dumps it down the sink?"

Dr. Koop said that he was concerned about "the next step, when Mrs. Jones decides she wants a child from that girl, blood gene pool down the block." He also said that he feared genetic manipulation to produce a "super race."

Dr. Haddon W. Robinson, chairman of the Department of Pastoral Missions at Dallas Theological Seminary, said that there was "no theological problem" with the English baby, but he said that he was afraid laboratory-fertilized eggs could be placed in "surrogate mothers," and that that would raise questions about "what it actually means to mother a child."

Giles Eccleston, secretary of the Church of England's Board for Social Responsibility, called the birth "an advance on meeting the problem of childlessness facing some married couples." But he said that he questioned the use of scarce medical resources for this when other needs, such as problems of the aged and the mentally handicapped, might be more pressing.

Cautious Catholic Reaction

Reaction from Roman Catholic authorities in England was also cautious. A statement by the Social Welfare Commission for the Church in England and Wales commended the birth as "a gentle expression of love," but it added that different cases posed a variety of problems.

Gordon Cardinal Gray, Archbishop of St. Andrews and Edinburgh, who is president of the Scottish Catholic Bishops, said that he had "grave misgivings about the methods and the possible implications and consequences for the future."

Ayatollah Milani, a Moslem Shiite leader in Iran, told an Iranian radio audience that a baby born under circumstances similar to those of the birth of England "is quite legitimate and legal" according to Moslem law "as long as the father and mother are husband and wife."

Rabbi Israel Klavan, an official of the Rabbinical Council of America, the major Orthodox group, said that Orthodox Jews would accept a baby born in this way.

And here she is...

THE LOVELY LOUISE

A Londoner looking at a photo of newly born Louise Brown on the front page of The Daily Mail

Doctors to a Baby Who Made Medical History

Patrick Christopher Steptoe and Robert Geoffrey Edwards

Special to The New York Times

LONDON, July 26 — The two men whose skill and ingenuity have achieved the first known birth of a baby conceived outside the body of a woman are acknowledged pioneers in their highly specialized fields.

Men in the News

Patrick Christopher Steptoe, 65 years old, has developed the technique whereby mature egg cells can be removed from a woman's ovary without major surgery so they can then be fertilized in glassware by sperm from the prospective father.

Robert Geoffrey Edwards, 52, has focused strongly about the extremely complex chemical messages that control the successive steps of reproduction to bring about normal development of an embryo even though fertilization was "in vitro" — in a glass vessel — and the resulting embryo was artificially inserted into the prospective mother.

Once Virtually Ostracized

While many in the medical community today were hailing the achievement, the work of the two men over a dozen years of collaboration had not always received so warm a reception. For a decade and a half, Dr. Edwards, in particular, fought rear-guard actions against cancellation of grants and against criticism from many quarters.

According to colleagues he was for a long time virtually ostracized by many of his peers and for more than a year dropped his research to explore its ethical and social implications.

The personalities of the two men are said to be very different. Dr. Edwards is described by co-workers as ebullient. Dr. Steptoe as more reserved 'and somewhat avuncular. Yet his career ship was reportedly shot out from under him in World War II, and he became a prisoner in Italy.

Dr. Edwards, who was born Sept. 27, 1925, comes of a farming family and retains a love of the soil that has reportedly led him to acquire land near Cambridge for small-scale farming. His interests also include politics. He has long served as a Laborite member of the Cambridge Town Council and for a time as chairman of its finance committee.

After studies at the University of Wales in Bangor, where he earned a doctorate in science, he obtained a Doctor of Philosophy degree at the University of Edinburgh and began to make a name for himself as a specialist in the physiology of reproduction.

From 1957 to 1958, he worked with the late Dr. Albert Tyler at the California Institute of Technology in Pasadena, then returned to the Institute of Animal Genetics in Edinburgh.

It was in the early 1960's that his activities began. By then he was at the National Institute for Medical Research at Mill Hill, London, trying with hormones to induce ovaries newly removed from women to produce mature egg cells. The ovaries had been obtained for a variety of medical reasons. The institute apparently saw his research as too controversial, and he departed for Cambridge, where he has worked ever since.

Ford Fund Aided Work

Beginning in 1963, the Ford Foundation became a prime supporter of reproduction research at Cambridge University's Marshall Laboratory, headed by Dr. Colin R. Austin. The foundation was particularly interested in research applicable to population control and contributed almost $1 million to the Cambridge effort.

It was Ford funds that enabled Cambridge to take on Dr. Edwards and provided his salary. However, in 1971 strong support of his research. The reason given was that his work did not seem to be contributing much to knowledge that could limit fertility.

A group of specialists sent to the university by the foundation to assess the program did not, however, agree with an evaluation by Britain's Medical Research Council, which had cut off its support. The American visitors felt, on the contrary, that Dr. Edwards's work met ethical standards for human experimentation.

His wife, Dr. Ruth Fowler, also at Cambridge, is a well known specialist in hormonal control of ovary function. They have five daughters.

Received 'Conjoint' Degree

Dr. Steptoe did his training at St. George's Hospital Medical School, one of 13 such schools operated by the University of London. In 1939, he won a "conjoint diploma." He became a member of the Royal College of Surgeons and was licensed by the Royal College of Physicians.

Almost immediately he was called to active duty in the Royal Navy Volunteer Reserve, and it was not until 1948, after his release from prison camp, that he was able to complete his postgraduate work and become a member of the Royal College of Obstetricians and Gynecologists. He is married and has a grown daughter and son and two grandchildren.

It is for his development of the technique for removing egg cells that he is known on both sides of the Atlantic. With this technique, called laparoscopy, a doctor inserts through a small subdominal incision near the navel a tubular device through which the entire operation can be performed.

The abdominal cavity is inflated with an inert gas to provide working room. Hairlike optical fibers threaded through the tube, or laparoscope, carry light to illuminate the ovary. Through additional fibers, the surgeon is able to maneuver a needle to select a ripe, or follicle," that contains a nearly mature egg. The follicle is then aspirated (withdrawn by suction) and the egg extracted.

INFANT IN BRITAIN REPORTED 'NORMAL'

Continued From Page A1

genetic engineering before a dictatorship tried to create a "master race."

The birth was not only a scientific breakthrough but also the high, or low, point of a headline race that tested the imagination of Britain's mass-circulation tabloid newspapers.

"It's a Girl," The Daily Mail announced above a picture of Mr. and Mrs. Brown in nightclothes. The Daily Mail is the leader of Associated Newspapers, the group that bought exclusive rights to the parents' story for a reported £200,000, which is about $370,000.

The rival Evening Standard trumpeted its own "test tube baby" this afternoon, reporting that another medical team had started trying to fertilize an egg from a London woman.

In a nation where paying news sources for the exclusive rights to a story is a common practice, the "test tube baby" story cost the winning newspaper group more than half a million dollars. It also touched off an angry debate over the practice, known as "checkbook journalism."

Some of the more conservatively run papers have deplored it. The editors of the popular papers have attacked the more conservative papers of self-righteousness.

The dispute intensified shortly after Associated Newspapers signed a contract with the Browns early this month. The Mail placed two guards at the door of Mrs. Brown's hospital room to keep out rival reporters. The hospital relented all news enquiries to Associated Newspapers in London.

Guards Were Withdrawn

But other news organizations protested so vehemently that the guards were withdrawn and the hospital authorities resumed answering questions.

Buying the story failed to guarantee exclusivity for The Mail and its sister publications, which include London's Evening News. Several rival papers have beaten them on secret details.

Doctor Doubts Ethics In Case of British Baby

The attempt to conceive a child outside the body, as in the recent British case reported that yielded a baby born a few days ago, was premature, according to a leading authority on the ethics of biomedical research said yesterday. But, he added, now that it has been demonstrated that an apparently healthy child can be produced that way, further attempts would appear to be ethical.

"The history of medicine is full of instances where things were done unethically but led to benefits for people," said Dr. Daniel Callahan, director of the Institute of Society, Ethics and the Life Sciences, based in Hastings-on-Hudson, N.Y.

Dr. Callahan, who conceded that his opinions were "not straightforward and simple," said that he based his view on the fact that the experiment was undertaken to benefit the prospective parents but that the risk of damage was borne by the child.

"Now that it has been done and it appears that it can be done safely, it appears to be justifiable," Dr. Callahan said.

SCIENTISTS ISOLATE GENE IN HUMAN CELL

Continued From Page A1

an inadequate supply of hemoglobin.

Dr. Stuart Orkin of Harvard said the image the team produced showed a row of fuzzy-looking black bands. If one or more bands was missing, that meant that part or all of the gene was missing.

Until now, he said, the only way to tell if a fetus had anemia was to take a sample of its blood and look for the hemoglobin itself, a risky procedure. The new technique allows doctors to take cells

Successful Laboratory Conception Intensifies Debate Over Procedures

Continued From Page A1

her ovaries, exposing it to sperm from her husband, allowing it to grow briefly in the laboratory, and then implanting it in her uterus.

A similar procedure was used at Columbia Presbyterian Medical Center in New York City in an attempt to enable a Florida woman to have a child. While still in the laboratory, the day-old embryo was destroyed, however. The couple, John and Doris Del Zio, sued the medical center, which replied that the experiment was clandestine and visionary to its regulations. A decision is pending in Federal District Court in Manhattan.

(Dr. Edwards, in response to his critics, has questioned why anyone should object to "giving these couples their own children," — a view reinforced by the exultant reaction of Lesley Brown and her husband, John.

Mr. Brown has been quoted by The Daily Mail, in a copyrighted article, as saying: "For a person who's been told he and his wife can never have children, the pregnancy was like a miracle." He said: "I felt 12 feet high," he said.

Most Similar Cases

Most cases that Dr. Edwards and Dr. Steptoe have treated in a dozen years of attempts have been those of women like Mrs. Brown and Mrs. Del Zio, whose products were inoperative because of blockage or another defect. It is in the oviducts, which carry mature egg cells from the ovaries to the uterus, that fertilization takes place.

One criticism of the Steptoe-Edwards treatment is that it surgically is not always preferable to cases of blocked or otherwise defective oviducts, which is believed to be the problem in 20 percent to 45 percent of infertile women. Dr. Edwards estimates, however, that surgery is likely in only about 17 percent of the cases.

The most controversial ethical problem associated with the Steptoe-Edwards method is the destruction of embryos that it may entail, although there are indications that in Mrs. Brown's case only one egg cell was extracted and thus only one embryo produced.

In some cases that Dr. Steptoe and Dr. Edwards have described, they used hormones to induce the prospective mother to produce a number of egg cells at the end of her monthly cycle.

Cultured in Laboratory

Several of these eggs were removed, exposed to sperm and then cultured in the laboratory until microscopic examination showed some of them subdividing as developing embryos.

One embryo that appeared normal was then injected into the woman's uterus through her cervix. The others, as one critic has put it, were "washed down the sink." It is this that has forced scientists to face the problem of when meaningful life begins.

One argument used in support of the method is that the laboratory procedure only mimics what nature does inside the reproductive system. It is estimated that a large percentage of embryos — some specialists say more than half — are shed by the body in the earliest stages of development.

A defective embryo, for example, may fail to transmit the chemical signal needed to stop monthly menstruation and create the conditions of pregnancy. Menstruation follows and the embryo is swept out.

Intrauterine devices, which are believed to prevent implantation in the uterus, and contraceptive pills are also said to cause contractions of the uterus that expel the embryo.

Challenged Critics' View

In the Quarterly Review of Biology, published at the State University of New York at Stony Brook, Dr. Edwards has sought to deal with his critics. In doing so he has challenged the view that human life begins at a single, sharply defined moment — that of fertilization.

In his article, entitled "Fertilization of Human Eggs in Vitro: Morals, Ethics and the Law," he contended that this step is but one in a continuing process. The thread of life, he proposed, runs unbroken from generation to generation. It is carried in the germ cells of a newborn infant girl, some of which will be fertilized to pass the germ plasm on to another generation.

'Demands Arbitrary Decisions'

"The assumption of full human rights at a single moment in a continuous developmental sequence," he wrote, "demands making arbitrary decisions that are unjustified biologically."

Some biologists contend that, in view of the process known as cloning, every cell of the body with a nucleus is a potential individual. When, for example, the nucleus is taken from the skin cell of a frog and placed in the egg of another frog whose nucleus has been removed, that egg can develop into a twin of the skin cell donor. In his article, however, Dr. Edwards said he saw little prospect for the use of cloning except in agriculture.

In response to those who said his work was opening the way for socially undesirable manipulations, he said that raising such research would be comparable to forgoing the development of airplanes because they made bombings and hijackings possible.

In addition to their attempts at implanting embryos conceived in the laboratory, Dr. Steptoe and Dr. Edwards have been studying the possibility of freezing and storing embryos, which, they say, could provide a "whole family" from a single egg-harvesting procedure. Other researchers, working with animals, have been experimenting with different methods of embryo implantation and genetic screening that could ultimately have an effect on research on humans.

Dr. Edwards did caution against other reproductive manipulations, although he said that donated semen was now "widely used." He said he envisioned, as well, the donation of egg cells for women unable to produce their own, but he noted the disputes and divided loyalties that can arise when a child's parentage is in doubt.

Another concern of the experimenters, and of others, is whether their technique selects inferior sperm and egg cells. Only a few sperm normally penetrate the reproductive system far enough to compete for fertilization, whereas in artificial insemination there is no such screening.

Those sperm that reach the goal naturally are "a highly selected sample," Dr. Edwards noted, "relatively free of genetic defects." Likewise, the egg cells that ripen under hormonal stimulation may not be those that would mature normally. Such subtle effects, if they exist, may not be evident until babies born by the Steptoe-Edwards method reach maturity.

Birth Defects Considered

If the Steptoe-Edwards procedure becomes commonplace, Dr. Edwards wrote, the situation "might well arise" in which a child is born with defects not evident in the parents. He cited a landmark case in which a deformed child and its parents sued a physician for allowing the child to be born.

Because birth defects occur even under the best of circumstances, he said, he would be hard to prove that the procedure was to blame. In transplants of animal embryos the birth defect rates have been no higher than normal.

At least one other British gynecologist is apparently trying to repeat the Steptoe-Edwards procedure. He is Ian Fergusson, an adjunct staff of Dr. Steptoe associate at Sir Thomas's Hospital in London. Press reports today told of his efforts to implant an embryo in a patient there.

Although many scientists in the United States reportedly are eager to begin similar experiments, they have been blocked from doing so until the National Ethics Advisory Board, formed in January to rule on human experimentation, takes action. The board has control over such research in any institution receiving federal funding for any of its activities.

The New York Times / Marilyn Church

Dr. Landrum B. Shettles being questioned by Michael Dennis, the lawyer for the plaintiff, at Federal District Court in Manhattan yesterday.

British Test-Tube Baby 'Unrelated' to Del Zio Case

By JUDITH CUMMINGS

Hoping the birth in Britain yesterday of the first conceived human "test-tube baby," a judge in Federal District Court in Manhattan cautioned the jury hearing Doris Del Zio's $1.5 million damage suit that the event had no bearing on her case.

News of the birth coincided yesterday with the first appearance as a witness of Dr. Landrum B. Shettles, a pioneer in in vitro fertilization and a central figure in the Del Zio case, as the trial continued into its eighth day.

A jury composing four women and two men was told by Judge Charles E. Stewart Jr. of Federal District Court that Tuesday's successful delivery of a baby girl to a British woman, Lesley Brown, [illegible] Her comment on the infant's reportedly normal condition was an apparent allusion to efforts by the defense in the Del Zio case to establish that a test-tube conception carries with it a substantial risk of producing an abnormal baby, as well as endangering the life of the mother.

'Like Evel Knievel'

Dr. Raymond L. Vande Wiele, the chief of gynecology at Columbia Presbyterian, who halted the Del Zio's fertilization attempt as an unsanctioned human experiment, rejected any suggestion that the success of the British medical team's efforts lent strength to the position of the Del Zios and their doctors that their own attempts would have succeeded.

"Nineteen seventy-three was a stunt, like Evel Knievel," he said. "Nineteen seventy-eight was a scientific achievement."

Dr. Shettles, who taught obstetrics and gynecology at the Columbia College of Physicians and Surgeons until leaving there in the controversy that followed his work with Mrs. Del Zio, took the witness stand in the afternoon to have a list of his publications and credentials read into the record by Michael Dennis, the plaintiffs' lawyer.

Mr. Dennis made a point of reading excerpts from a book review of "Ovum Humanum," Dr. Shettle's 1960 work on the development of the human ovum, written by Dr. John Rock, a gynecologist who is credited with developing the first effective oral contraceptive. Dr. Rock called the book "a towering tribute to the dedicated ardor of a careful, resourceful, scholarly workman."

Assisted Reproduction

- Developed largely out of sight (and the US)
- Ethical outcry rapidly subsided as success of procedure became apparent
- Little regulatory oversight developed and further advances occurred largely in the private sector
- Created market for gametes
- Has provided many women, and couples, the potential to have children that they might otherwise not have

Business Week, November 18, 1985

Cover Story

THE GENE DOCTORS

SCIENTISTS ARE ON THE VERGE OF CURING LIFE'S CRUELEST DISEASES

A STARTLING NEW MEDICAL TECHNIQUE COULD RESCUE TARA DEW FROM A LIFE OF LONELINESS

More than anything else, Tara Dew would like a puppy. That's not unusual for a nine-year-old girl. But for Tara, a pet could be fatal. She is a victim of ADA deficiency, the inherited immunological disease that killed David, the famous "Bubble Boy." Although her disease is not as severe as David's, a stray virus picked up from any animal or person could mean death. As a result, Tara cannot go to school. She must stay in her home in Bellevue, Neb., listening via a speakerphone to classes going on in a local schoolroom. Her few playmates must be carefully screened for sniffles and chicken pox. And once a month she must endure lengthy blood transfusions to give her some small but crucial resistance to disease.

Tara's malady might be helped by a bone-marrow transplant. The new marrow would produce the missing enzyme—adenosine deaminase, or ADA—from which her disease takes its name. But the transplant is risky, and it could even be fatal. So even though Tara is living on borrowed time—few ADA children live past the age of two—Tara's parents are holding out for a startling new development called gene therapy. Instead of implanting marrow cells from a donor, doctors would go directly to the root of Tara's problem and replace the defective gene in her own marrow.

GREEN LIGHT. Just a decade ago, the prospect of manipulating human genes was almost inconceivable. Scientists were just beginning to decipher the tangle of deoxyribonucleic acid, or DNA, that carries the hereditary coding for organisms. But the pace of the research has been astonishing. In the late 1970s, they first put human genes into bacteria, turning them into factories for useful proteins. Then, in 1982, researchers altered the genes of a higher animal. Scientists at the University of Pennsylvania created a huge "Supermouse" by transplanting a gene for rat growth hormone into a mouse embyro.

Gene Therapy

Gene Therapy

- Attempt to introduce expressible genes (DNA) into somatic cells in effort to correct or modulate function(s)
- Challenge in “engineering” as well as biology
- Initially envisioned to be most useful for inherited disorders, e.g. sickle cell anemia, immune deficiencies (largely of the blood system)
- Soon thereafter, proposed for other inherited disorders, e.g. cystic fibrosis, muscular dystrophy
- Largest initial clinical efforts early on turned out to be in infectious disease (AIDS) and cancer

The Crime of Scientific Zeal

1981

The reprimand by the National Institutes of Health of a California scientist who performed improper gene-splicing experiments has broad symbolic importance. More is at stake here than the misconduct of Dr. Martin Cline of the University of California at Los Angeles — apparently the first scientist to insert controversial "recombinant DNA" molecules into humans.

Few fields of research excite so much public interest and apprehension. When first discovered, the splicing of genes from different organisms into new recombinant genes led many scientists to fear the inadvertent production of new organisms, even monsters capable of causing devastating epidemics or disrupting human evolution. Federal guidelines were written to regulate the research.

Most scientists have since concluded that the risks are slight and the potential benefits — in medicine, agriculture and industry — enormous. But they respect the public's concern and discipline themselves accordingly.

Dr. Cline's experiments violated this restraint. His goal was laudable: to treat painful, incurable and often fatal blood diseases, like beta-thalassemia and sickle cell anemia. They are caused by genetic defects that might be repaired by introducing normal genes into the patient's bone marrow cells. The genes might be pure or in a recombinant form with other genes — maybe those of a virus, which increase the chances of success but also the risk.

A university review committee stopped Dr. Cline from using pure genes until he had performed more animal tests. In Israel, however, a similar committee agreed to human tests. But at the last minute, without telling anyone, Dr. Cline used recombinant genes, about which the Israelis had expressed particular concern. He then moved on to Italy and inserted recombinant genes in a second patient, apparently satisfying less exacting standards there.

No one was hurt, but there is no evidence that the patients were significantly helped or that science was advanced. Dr. Cline has been forced to resign a university division chairmanship, and the National Institutes of Health will henceforth show the most exacting care in monitoring his work.

He was rightly punished. And the public should feel reassured. If scientists expect to keep pursuing their studies without undue political interference, they can keep only one eye on the microscope. The other should look around. The freedom of science is inseparable from the public trust in science.

Chicago Tribune
$1.00 Sunday, March 2, 1986 Final Edition

Sunday

Spring fashions and the FBI burglars

There are two big magazines in today's Tribune: SUNDAY Fashion with the newest and the hottest for spring, and the regular SUNDAY magazine with a revealing report on FBI burglaries.

Behind the scenes

It's terrorism vs. tourism in Europe

Fear of terrorists is keeping a lot of Americans from visiting Europe this year. In Travel.

Robot highways

On the automated highways of the future you'll be able to nap while computers guide your car. In Tomorrow.

'Big River' rolls in

"Big River," the musical version of "Huckleberry Finn," is rolling into Chicago. Sid Smith tells how it all began. In The Arts.

Photo by Peter Miller, The Image Bank/Chicago

Sports

Georgia Tech dumped by Illinois

Hernandez to challenge drug ruling

Dunston is ready, so are Sox catchers

Gene therapy reshaping our future

By Jeff Lyon
and Peter Gorner
Chicago Tribune

BETHESDA, Md.—In a laboratory here on the sprawling campus of the National Institutes of Health, an experiment is underway that could change the face of medicine forever.

Reduced to its barest details, the experiment sounds hardly momentous, and possibly eccentric, or even cruel. Since early September, researchers have been drawing bone marrow from rhesus monkeys, deliberately infecting it with cancer virus and injecting it back into the monkeys' bloodstreams.

But the goal is not to give the monkeys cancer. In fact, the virus has been altered so that it will not cause tumors. The goal is to alleviate human disease—and do it with a power that has heretofore been reserved for the gods.

If the research leader, W. French Anderson, gets the results he hopes for, then sometime in the coming months he will apply for permission to try the same experiment on a different kind of test subject: a human child.

The procedure would represent a scientific milestone of incalculable magnitude. It would mark the first authorized attempt at human gene therapy—a bold attack on inherited disease at its very source.

ALTERED FATES

Scientists are nearing a breakthrough in gene research that may offer hope to patients like Alison Ashcraft who suffer from a host of devastating genetic diseases. A 7-part series begins in Tempo.

In an extraordinary coming-together of the latest discoveries in biology and genetics, researchers are gearing up to undertake something that would have seemed like science fiction less than five years ago. They hope to break into a patient's cells and replace a malfunctioning gene.

In all probability, the initial experiment will be aimed at a rare genetic defect called ADA deficiency, the disease that led to the death of Houston's famous "Bubble Boy" and that destroys a child's immune system.

But if successful, the technology ultimately may be applied to a vast array of hereditary diseases that exact a huge toll in human suffering and economic dislocation.

Many genetic researchers foresee a day when such inherited killers and disablers as cystic fibrosis, muscular dystrophy, hemophilia, sickle cell anemia, beta thalassemia, Tay-Sachs disease, phenylketonuria [PKU], Huntington's chorea and neurofibramatosis [Elephant Man's disease] may be treated and cured by gene therapy.

Such disorders, all caused by an error in just one of the thousands of genes that each of us carries in our cells, have remained stubbornly resistant to the progress made in other areas of modern medicine.

Gene therapy may also be enlisted one day in the fight against a number of other human ills, including heart disease, cancer and even schizophrenia.

Nevertheless, researchers caution that gene therapy is in its embryonic

Continued on page 18

Sweden stunned by killing

Late-hour tavern issue spread

Assassin of premier eludes hunt

By Ray Moseley

March 2, 1986


A NEW DAWN WITH GENE THERAPY!
LAND OF MILK AND HONEY —VIA GENE TRANSFER
NOT YET, THOUGH.
NOW, LET'S ALL CALM DOWN A BIT.
NIH
NIH
B.

Gene Therapy 'Oversold' By Researchers, Journalists

NIH Advisers Cite Nearly Uniform Failure

By David Brown
Washington Post Staff Writer

Gene therapy as a treatment for human diseases has been "oversold" by scientists and the news media even though it has been a nearly uniform failure, a panel of scientific advisers told the head of the National Institutes of Health yesterday.

Although the manipulation of genes will almost certainly prove useful sometime, huge gaps of knowledge must be filled in before it becomes a practical form of treatment. More effort should be devoted to answering questions in the laboratory, and less to trying out long-shot therapies in patients, the panel suggested.

"Strict adherence to the highest standards of excellence in clinical [experiments] must be demanded," Stuart H. Orkin, one of the panel's chairmen, told a meeting of top NIH officials. "Inherent in that is the suggestion that we don't think that's been the case so far."

Although couched in the decorous and circumspect language of science, the panel's report is a stern critique of virtually everyone involved in gene therapy.

Researchers were chided for, in some cases, jumping immediately from the discovery of a "disease gene" to trying gene therapy, without first using the newfound knowledge as groundwork for more conventional treatments. Heads of NIH's many institutes were cautioned against promoting mediocre gene therapy projects just for the status they confer. Both the news media and research establishment were accused of exaggerating gene therapy's "promise" to a gullible public.

Genes, made of DNA, reside permanently inside nearly all cells.

See NIH, A22, Col. 1

NIH review of gene therapy 1995

The New England
Journal of Medicine

VOLUME 346 APRIL 18, 2002 NUMBER 16

SUSTAINED CORRECTION OF X-LINKED SEVERE COMBINED IMMUNODEFICIENCY BY EX VIVO GENE THERAPY

SALIMA HACEIN-BEY-ABINA, PH.D., FRANÇOISE LE DEIST, M.D., PH.D., FRÉDÉRIQUE CARLIER, B.S., CÉCILE BOUNEAUD, PH.D., CHRISTOPHE HUE, B.S., JEAN-PIERRE DE VILLARTAY, PH.D., ADRIAN J. THRASHER, M.D., PH.D., NICOLAS WULFFRAAT, M.D., RICARDO SORENSEN, M.D., SOPHIE DUPUIS-GIROD, M.D., ALAIN FISCHER, M.D., PH.D., AND MARINA CAVAZZANA-CALVO, M.D., PH.D.

Science, March, 2005

GENE THERAPY

Panel Urges Limits on X-SCID Trials

A U.S. advisory committee last week recommended limits on gene therapy trials in light of a third case of leukemia in a study in France. The panel suggested that U.S. studies of the same disease, X-linked severe combined immunodeficiency (X-SCID), should enroll only patients for whom conventional treatment has failed. However, trials of related diseases, as well as gene therapy trials using similar retroviral vectors, should continue, the panel said. The third leukemia "doesn't change the sense of unease dramatically," said chair Mahendra Rao of the National Institutes of Health (NIH).

Gene therapy trials for SCID have been the field's only success; since 1999 gene therapy has restored the immune systems of at least 17 children with two forms of the disorder. Excitement turned to worry in late 2002, however, when two children developed T-cell leukemia in a trial of X-SCID led by Alain Fischer at the Necker Hospital in Paris; one child died last fall. Although trials put on hold later resumed, a report that a third child in the French trial developed leukemia in January rekindled concerns about the therapy's risks (*Science*, 18 February, p. 1028).

This latest leukemia appears to be different from the previous two. Those occurred after a retrovirus carrying a gene called *gamma c* inserted into the oncogene *LMO2* in bone marrow cells in infants less than 3 months old, noted Food and Drug Administration (FDA) official Carolyn Wilson at a meeting of the FDA Cellular, Tissue, and Gene Therapies Advisory Committee. According to data provided by Fischer and French authorities, the third child, who was treated at 9 months old, does not appear to have an *LMO2* insertion. Although the vector again apparently landed on an oncogene or oncogenes, the insertions occurred at three sites that have not yet been identified.

Success story. Christopher Reid, a patient in a British X-SCID gene therapy trial.

The panel also heard other new data, which offered a mixed message. Last September, a monkey died from a leukemialike cancer at NIH, apparently as a result of being treated in 1999 with a retrovirus carrying two marker genes, reported Cynthia Dunbar of NIH. On the other hand, NIH's Utpal Davé described a report last year in *Science* on a retrovirus-induced mouse ▶

Complication of gene therapy for immune deficiency: acute T-cell leukemia

REPORT AND RECOMMENDATIONS OF THE PANEL TO ASSESS THE NIH INVESTMENT IN RESEARCH ON GENE THERAPY

Stuart H. Orkin, M.D.
Arno G. Motulsky, M.D.

Co-chairs

December 7, 1995

"Because clinical experience is still so limited, it is not possible to exclude longterm adverse effects of gene transfer therapy, such as might arise from mutations when viral sequences randomly integrate at critical sites in the genome of somatic cells. It must be noted that multiple integration events resulting from repeated administration of large doses of retroviruses theoretically pose a risk for leukemic transformation. Only longitudinal clinical followup of treated patients can provide data on the long term safety of gene therapy protocols."

Gene Therapy: where are we now?

1. We know it “works” in the proper clinical setting with fastidious attention to detail
2. But, as with all therapies, we appreciate that there are serious, potential complications, some of which could have been anticipated
3. Some promising findings in other type of X-SCID and in host defense disorder (chronic granulomatous disease) and also in forms of hemophilia
4. Prediction: gene therapy will ultimately find a place in medicine, but applications for the foreseeable future are likely to be limited to rare disorders, rather than more common diseases
5. Prospects may change radically *IF* methods are developed to <u>correct</u> genes *in situ* rather than merely add genes randomly, as done to date
6. Timeframe: to date, >25 yrs with checkered success

Comparisons of stem cell field to others

1. As with BMT, assisted reproduction, and gene therapy, potential for large, positive impact on human health exists
2. More than BMT or assisted reproduction, stem cell research is conducted under the “microscope” of the public
3. Regulatory oversight (ie guidelines) introduced earlier in evolution of the field
4. Intellectual property involvement also introduced earlier: will this inhibit applications?

Highest priority areas for stem cell field

1. Identifying and characterizing stem cells in different organ systems: Are there stem cells? How to isolate them and study their properties and capabilities? What is the niche of stem cells in different organs?
2. Delineating pathobiology of target diseases: What is the role of stem cells? What might stem cells (and/or their descendents) offer?
3. Elucidating self-renewal in stem cells: harness cellular reprogramming and directed differentiation
4. Developing real-time, informative methods for examining fate, behavior and function of stem cells following introduction into animal models or patients: experiments must inform science, not just “yes or no”

Challenges going forward

1. Developing the infrastructure for proper characterization, maintenance, and expansion (or differentiation) of stem cells for clinical use (not only lab but also regulatory and intellectual property infrastructure)
2. Designing *preclinical* studies that provide maximum, *relevant* data for considering transition to the clinic
3. Designing *clinical* studies that provide real-time surrogate measures of *in vivo* effects
4. Balancing the prospects for success and the realities of potentially inadequate therapy or serious “side-effects” in treating life-threatening or debilitating disorders

Challenges going forward

1. Stem cell infrastructure: embryonic stem cell bank, training center(s), exploration of alternative means of embryonic stem cell generation, antibodies for prospective isolation of subsets of cells and adult stem cells, GMP lab(s) for cell expansion
2. *Preclinical* studies: *appropriate* animal models of diseases, imaging of introduced cells, “animal hospital”, toxicology
3. *Clinical* studies: fastidious design with real-time surrogate measures, “translational lab(s)” for assays of relevant biomarkers, careful but balanced oversight, registry, involvement of pharma expertise and support